



#4

Rec'd PCT/PTO 05 SEP 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Nicholas Bachynsky

Woodie Roy

Serial No.: 09/744622 (PCT/US99/16940)

Filed: January 26, 2001

For: **CHEMICALLY INDUCED**
INTRACELLULAR HYPERTHERMIA§
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Group Art Unit: Unknown

Examiner: Unassigned

Atty. Docket: P01615US1 / 09805783
(U.S. Nat'l. Phase)

RECEIVED

19 SEP 2001

Logan Staff
International Division

PETITION UNDER 37 CFR 1.47

Texas Pharmaceuticals, Inc., assignee of the whole interest in the above-referenced invention, respectfully requests that a declaration signed by assignee be accepted in fulfillment of the Notification of Missing Parts Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office mailed March 5, 2001. The inventors in the above-referenced application have refused to execute a current Declaration in this application after numerous attempts have been made to have them execute one, although they signed one when the provisional application on which the above-identified application is based was filed. Their refusal apparently stems from a dispute between them and the owner of the application, Texas Pharmaceuticals, Inc.. The inventors executed assignments of the invention to Texas Pharmaceuticals, Inc., copies of which are attached as Exhibit A. The earlier signed declaration is attached as Exhibit B. The general attorney for Texas Pharmaceuticals, Inc. advised the undersigned that the inventors would not sign a current declaration and refused to accept letters by certified mail.

Thus, in order to preserve the rights of the parties and to prevent irreparable harm by allowing the application to become abandoned, it is necessary to accept a declaration signed by

25015073.1

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01 FC:154

130.00 CH

the assignee of the application, Texas Pharmaceuticals, Inc. prior to the expiration of the time period set for submission.

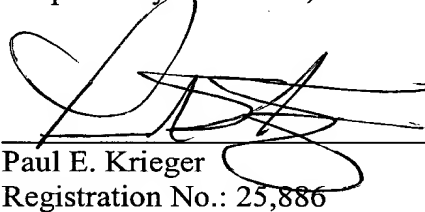
The last known addresses of the inventors are:

Nicholas Bachynsky
5944 Coral Ridge Drive, Suite No. 202
Coral Springs, FL 33076

Woodie Roy
5944 Coral Ridge Drive, Suite No. 202
Coral Springs, FL 33076

Please charge the deposit account of Fulbright & Jaworski LLP, Account No. 06-2375, for the petition fee of \$130.00 and any additional fees that may be necessary.

Respectfully submitted,


Paul E. Krieger
Registration No.: 25,886

09/13/2001 SNAJARRO 00000073 062375 09744622
01 FC:122 130.00 CH

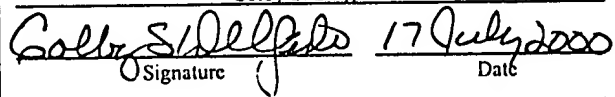
Date:

Sept. 5, 2001

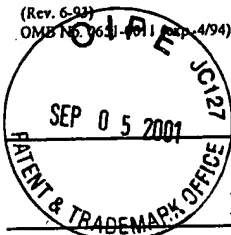
FULBRIGHT & JAWORSKI L.L.P.
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
Phone: (713) 651-7732
FAX: (713) 651-5246



Exhibit 1



FULBRIGHT & JAWORSKI L.L.P.
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
Phone: 713-651-8231
Facsimile: 713-651-5246



RECORDATION FORM COVER SHEET

To the Honorable Commissioner of Patents and Trademarks:
Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Nicholas Bachynsky

Additional name(s) of conveying party(ies) attached?

☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Texas Pharmaceuticals, Inc.

Internal Address: _____

Street Address: 701 W. 4th Street

City: Texarkana

State: TX Zip: 75501

3. Nature of Conveyance:

☒ Assignment ☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Additional name(s) & address(es) attached?

☐ Yes ☒ No

Execution Date: March 4, 1998

4. Application number(s) or patent number(s): PCT/US99/16940

If this document is being filed together with a new application, the
execution date of the application is: _____

A. Patent Application No.(s): _____

B. Patent No.(s) _____

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence
concerning document should be mailed:

Name: David L. Fox

Internal Address: Fulbright & Jaworski LLP

Street Address: 1301 McKinney

Suite 5100

City: Houston

State: TX Zip: 77010-3095

6. Total number of applications and patents involved:
1

7. Total fee (37 CFR 3.41): \$ 40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number: _____

(Attach duplicate copy of this page if paying by deposit account)

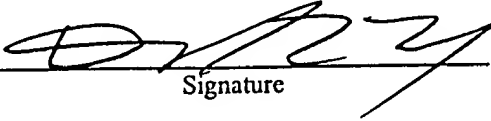
DO NOT USE THIS SPACE

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David L. Fox

Name of Person Signing


Signature

17 July 2000

Date

Total number of pages including cover sheet, attachments, and document. **8**

Mail documents to be recorded with required cover sheet information to:

ASSIGNMENT

DATE: March 4, 1998

ASSIGNOR: NICHOLAS BACHYNSKY
701 W. 14th Street
Texarkana, Texas 75501

ASSIGNEE: TEXAS PHARMACEUTICALS, INC., a Texas corporation
701 W. 14th Street
Texarkana, Texas 75501

In consideration of Ten Dollars (\$10.00) cash in hand paid to me and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I, NICHOLAS BACHYNSKY (hereinafter called "Assignor"), who have made an invention of a novel use and method of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, assign, sell, transfer and convey to TEXAS PHARMACEUTICALS, INC., a Texas corporation, whose address is 1314 Main Street, Texarkana, Bowie County, Texas 75501 (hereinafter called "Assignee"), its successors and assigns, Assignor's entire right, title and interest in and to the following rights, interest, and property (hereinafter collectively called the "Rights"):

1. Assignor's invention of uses, methods and therapies of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, including without limitation Assignor's rights, powers, interests and title in and to the methods, uses and processes described in Schedule 1 attached to this Assignment, (collectively, herein called the "Invention").
2. All applications for patent or like protection on said Invention that have been

or may in the future be made by Assignor or Assignor's legal representatives, in any and all countries.

3. All patents and like protection that have been or may in the future be granted on said Invention to Assignor or Assignor's legal representatives, in any and all countries of the world.
4. All substitutions for and divisions, continuations, continuations-in-part, renewals, reissues, extensions and the like of said applications and patents and similar rights or grants, including, without limitation, those obtained or permissible under past, present and future law and statutes.
5. All rights of action on account of past, present and future authorized or unauthorized use of said Invention and for infringement of said patents and like protection.
6. The right of Assignee to file in his name disclosure documents, applications for patents and like protection for said Invention in any country and countries in the world.
7. All international rights of priority associated with said Invention, disclosure filings, applications, patents and like protection.

TO HAVE AND TO HOLD the Rights unto the Assignee, its successors and assigns forever, and Assignor does hereby bind himself, his heirs, legal representatives and assigns, to forever WARRANT and DEFEND the title to the Rights unto the said Assignee, its successors and assigns, against any person whomsoever lawfully claiming, or to claim the same, or any part thereof.

Assignor covenants and agrees that Assignor will cooperate with Assignee such that Assignee may enjoy to the fullest extent the benefit of this Assignment. Such cooperation shall include, but not limited to, all of the following:

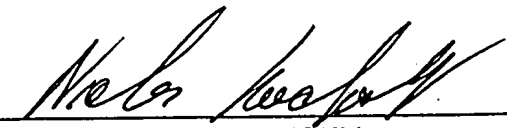
1. Assignor's prompt execution of all papers that are deemed necessary or desirable by Assignee to perfect the right, title and interest herein conveyed, and
2. Assignor's prompt execution of all petitions, oaths, specifications, declarations

or other papers that are deemed necessary or desirable by Assignee for filing and prosecuting patent applications, for filing and prosecuting substitute, division, continuing, or additional applications in the United States and/or all foreign countries, for filing and prosecuting applications for reissuance or reexamination of letters patent, and for interference proceedings involving and covering any of the Rights, and

3. Assignor's prompt assistance and cooperation, including but not limited to execution of documents and testifying, in the prosecution of legal proceedings involving any of the Rights, including, but not limited to, patent prosecution, interference proceedings, infringement court actions, opposition proceedings, cancellation proceedings, priority contests, unfair competition court actions, trade secret court actions, public use proceedings, slander, license breach and royalty collection proceedings and other legal proceedings.

Assignor warrants that Assignor has the right to make the assignment set forth herein and that no other person or entity has any rights of ownership or claim to the subject matter of this Assignment. This Assignment is binding upon Assignor, Assignor's heirs, administrators, executors, successors, trustees, devisees and assigns and inures to and for the benefit of Assignee, its successors and assigns.

EXECUTED effective as of the date first above written and at the time and place indicated below opposite the signature:



NICHOLAS BACHYNSKY
Date: 3/4/98

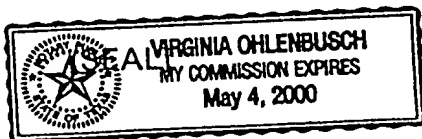
STATE OF TEXAS

§
§
§

COUNTY OF BEXAR

BEFORE ME, the undersigned authority, on this day personally appeared NICHOLAS BACHYNSKY known to me to be the person whose name is subscribed to the foregoing instrument, and acknowledged to me that he executed the same for the purposes and consideration therein expressed.

GIVEN UNDER MY HAND AND SEAL OF OFFICE, this the 5th day of March, 1998.



Virginia Ohlenbusch
Notary Public Signature

Virginia Ohlenbusch
Notary Printed Name

Commission Expires: 5-4-2000



SCHEDULE 1 TO ASSIGNMENT

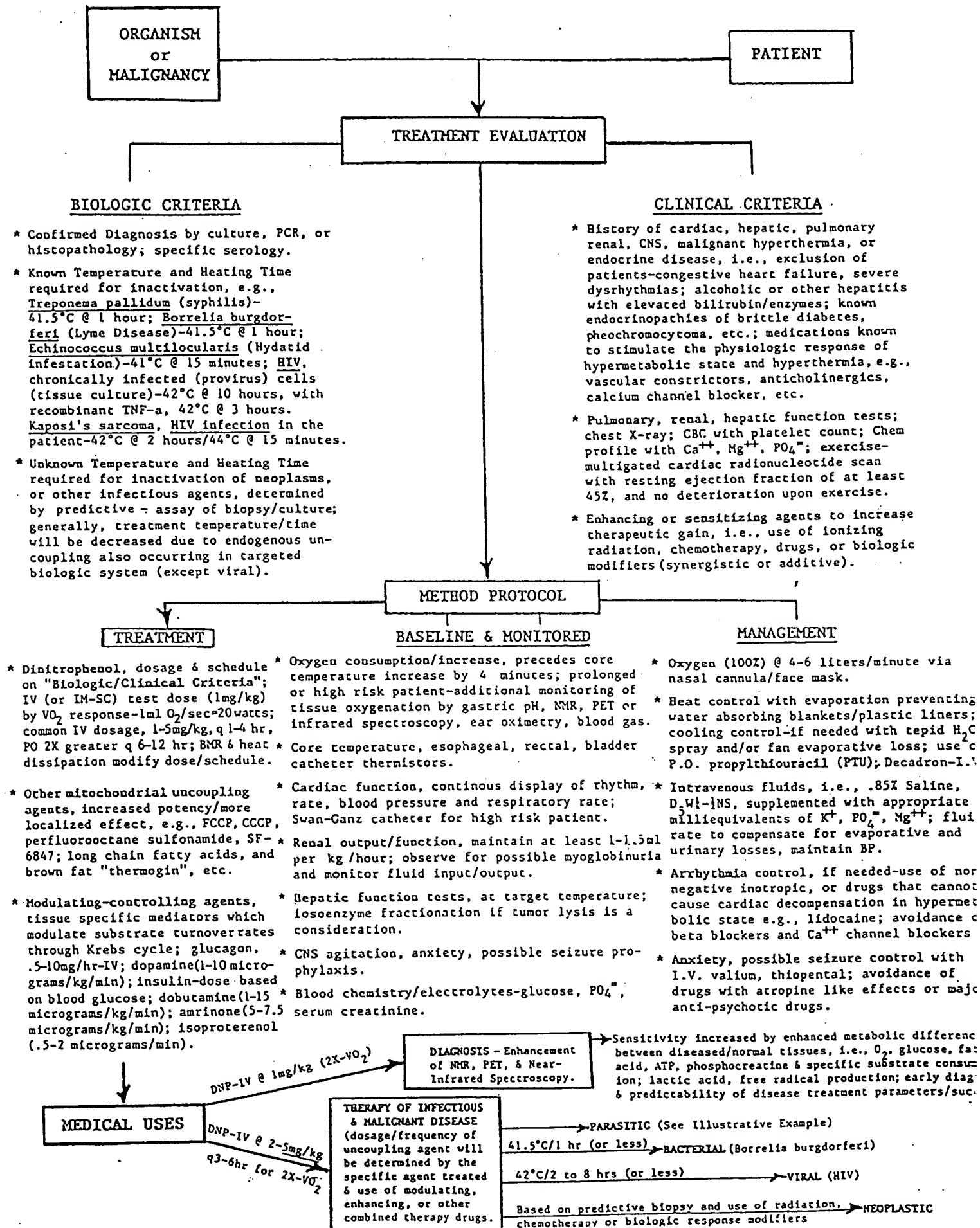
INVENTION

This invention provides a medical method for: (1) prevention of life threatening hypothermia; (2) enhancing magnetic resonance spectroscopy and positron emission tomographic metabolic imaging; and (3) treatment of resistant neoplastic and infectious disease by concurrent administration of dinitrophenol [or other mitochondrial thermoregulatory uncoupling agents, e.g., carbonylcyanide m-chlorophenylhydrazone (CCCP), carbonylcyanide-p-trifluoromethoxy-phenylhydrazone (FCCP), recombinant brown fat type protein, or lipid proton ionophores] and respiratory oxygen, intravenous fluids, anti-platelet drugs, as needed cooling, and specific metabolic, activating cytokines [e.g., recombinant tumor necrosis factor (TNF), interferons, etc.], hormones (e.g., glucagon), and other medications to control and focally enhance the mitochondrial uncoupling effects.

The present invention avoids the use of labor intensive, complex hyperthermia equipment, including invasive extracorporeal perfusion, with its associated thermal gradient toxicity problems to interposed normal tissues, inherent to all therapeutic methods of delivering heat from the outside-in. A new use(s)/method of generating intracellular oxygen derived free radicals, and heating from within the cell has been discovered for dinitrophenol (or other oxidative phosphorylation uncouplers) in prevention of cold injury, and treatment of free radical-thermosensitive parasites (e.g., Echinococcus), bacteria (e.g., Borrelia burgdorferi), lipid enveloped viruses (e.g., HIV), and neoplasia (e.g., gastric adenocarcinoma). It has further been discovered that cataracts, induced by dinitrophenol in the treatment of chronic obesity, can be prevented by concomitant administration of a variety of free radical scavenging agents, including tocopherol, ascorbic acid, and beta-carotene.

Briefly, the present invention is a new use(s)/method of inducing increased, intracellular free radical flux and hyperthermia, including the procedure of administering dinitrophenol to patients in doses sufficient to denature and inactivate targeted biologic systems. Concurrent administration of tissue selective activating hormones, biologicals or drugs permits greater enhancement of the therapeutic index, while physiologic gain cooling, fluids, respiratory oxygen, and monitoring procedures permit safe therapeutic control. The figure on the attached page depicts an example use(s)/methodology of this process in an algorithm.

SCHEMATIZED MITOCHONDRIAL UNCOUPLING METHOD FOR DIAGNOSIS & TREATMENT OF INFECTIOUS AND MALIGNANT DISEASE



ILLUSTRATIVE METHOD/USE EXAMPLE

A 52 year old white Swiss male, hunting dog trainer, presented with right upper quadrant abdominal pain. History revealed past(24 month old) hepatic "cyst" surgery and treatment with albendazole(only 1 dose was given because of anaphylactic reaction). He denied history of weight loss, pulmonary, cardiac or neurologic disease. Upon physical examination, he had a weight of 198 pounds (90 Kg), height of 5'11", blood pressure 140/80, pulse-76 and regular, respirations 18/minute, and oral temperature of 37.3°C. Laboratory studies, including hepatic, renal, pulmonary and cardiac function tests were normal; complete blood count was unremarkable except for 20% eosinophilia. Ultrasound and nuclear magnetic resonance of the liver revealed 4 (2-3 cm. in diameter) cysts in the mid-right lobe; ELISA serology showed a diagnostic titer specific for Hydatid disease with Echinococcus multilocularis. The patient refused to entertain any additional surgery or albendazole therapy.

After clinical assessment and treatment evaluation, i.e., Echinococcus multilocularis protoscoleces and germinal layers are destroyed at 41°C/15 minutes, whereas liver-hepatocytes withstand temperatures of 42°C to 44°C for known periods of 20 hours and 15 minutes respectively, the patient was given 1 aspirin; 10 mg. diazepam by mouth; and, intravenous fluids of 0.85 normal saline containing 9 millimolar K_2PO_4 , 7 milliequivalents of K^+ , and 2cc of 50% saturated solution of Mg_2SO_4 /liter, were infused at a rate of 12cc/kg/hr. Urine output was maintained at 1cc/kg/hour or greater. Esophageal (optional), rectal and foley (16 gauge) tipped bladder catheter thermistors gave temperature readings every two minutes within 0.1°C. Cardiac rate, rhythm, blood pressure, and respiratory rate sensors were placed and continuously displayed on a multi-channel monitor. Intravenous glucagon-2mg/hr was infused, with 1 mg given prior to DNP.

The patient was covered with a water absorbing polyethelene lined blanket, and baseline respiratory gas flow/oxygen consumption (VO_2) was determined using a 3 minute bag collection. Five minutes after intravenous administration of 90 mg of dinitrophenol (2% DNP/5% $NaHCO_3$ at 1 mg/kg), and determination that there was no untoward or idiosyncratic reaction, an additional 90 mg of 2,4 dinitrophenol (total of 180mg, 2mg/kg body weight) was infused. Monitored physiologic parameters are shown in the Table below. An additional VO_2 rate was obtained five minutes after the second dose of DNP and the patient was thereafter placed on 100% O_2 via nasal cannula. Target core temperature was maintained by occasional exposure of a limb and/or decreasing the glucagon infusion rate to 0.25 mg/hour. After the patient was maintained at a core temperature of 41.3°C for 20 minutes, the treatment was terminated by removing the blanket and permitting evaporative and radiant heat loss to return the body temperature to a normothermic level.

TABLE

Monitored Clinical Data On Mitochondrial Uncoupling Use/Method In Illustrative Example
(Treatment of Hydatid disease-Echinococcus multilocularis)

Time (minutes)	Medication (type & dose)	Resp. Rate- O_2 Consumption (breaths/min) ²	Cardiac Rate (beats/min)	Urine Output (total ml)	Core Temp. (°C)	Other (remarks)
-60	I.V. Fluids - .85% NS @ 0.8 L/hour	18	78	-	37.1	Fluids @ 10-12cc per kg/hour.
-30	Glucagon-IV Drip @ 2mg/hour	20	78	47	37.1	Hepatic Krebs Cycle stimulation.
0	2,4-dinitrophenol-90mg IV in 4.5ml of 5% $NaHCO_3$	20	88	58	37.4	Covered with polyethylene blanket.
2	[prepared by dissolving 2.3gm DNP(15% H_2O) in 5% $NaHCO_3$ -giving 2% solution]	24	92	-	37.8	Increased O_2 consumption precedes temp. elevation.
5	2,4-dinitrophenol-90mg IV in 4.5ml of 5% $NaHCO_3$	26	98	-	37.8	
10	Fluids increased to 1.2 L/hour; start O_2	30	110	15	39.4	After VO_2 determined 100% O_2 @ 4 L/min via nasal cannula.
20	-	30	120	18	40.3	
40	Glucagon -IV Drip decreased to 0.5mg/hr	30	138	28	41.4	Lower extremity is partially exposed.
60	Glucagon discontinued	30	140	30	41.2	Blanket removed
120	IV fluid discontinued	24	100	98	38.4	All thermistors removed

1/ Variations of the above use/method, i.e., protocol evaluation, monitoring, medications/dosages, time & temperature of mitochondrial uncoupling, will be necessitated by clinical and targeted biologic system treatment factors. Such variations for treatment of other parasitic (e.g. Malaria), bacterial (e.g., Lyme, Hansons disease), viral (e.g., HIV) and neoplastic disease will occur to those skilled in the art of medicine, and will be more fully described in the patent application.



RECORDATION FORM COVER SHEET

To the Honorable Commissioner of Patents and Trademarks:
Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Woodie Roy

Additional name(s) of conveying party(ies) attached?

☐ Yes ☒ No

2. Name and address of receiving party(ies):

Name: Texas Pharmaceuticals, Inc.

Internal Address: _____

Street Address: 701 W. 4th Street

City: Texarkana

State: TX Zip: 75501

3. Nature of Conveyance:

☒ Assignment

☐ Merger

☐ Security Agreement ☐ Change of Name

☐ Other _____

Execution Date: July 21, 1998

Additional name(s) & address(es) attached?

☐ Yes

☒ No

4. Application number(s) or patent number(s): PCT/US99/16940

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s): _____

B. Patent No.(s) _____

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: David L. Fox

Internal Address: Fulbright & Jaworski LLP

Street Address: 1301 McKinney

Suite 5100

City: Houston

State: TX Zip: 77010-3095

6. Total number of applications and patents involved:
2

7. Total fee (37 CFR 3.41): \$ 40.00

☒ Enclosed

☐ Authorized to be charged to deposit account

8. Deposit account number: _____

(Attach duplicate copy of this page if paying by deposit account)

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9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

David L. Fox

Name of Person Signing

[Signature]
Signature

17 July 2000

Date

Total number of pages including cover sheet, attachments, and document. 8

Mail documents to be recorded with required cover sheet information to:

ASSIGNMENT

DATE: July 21, 1998

ASSIGNOR: WOODIE ROY
c/o 701 W. 14th Street
Texarkana, Texas 75501

ASSIGNEE: TEXAS PHARMACEUTICALS, INC., a Texas corporation
701 W. 14th Street
Texarkana, Texas 75501

In consideration of Ten Dollars (\$10.00) cash in hand paid to me and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I, WOODIE ROY (hereinafter called "Assignor"), who have made an invention of a novel use and method of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, assign, sell, transfer and convey to TEXAS PHARMACEUTICALS, INC., a Texas corporation, whose address is 1314 Main Street, Texarkana, Bowie County, Texas 75501 (hereinafter called "Assignee"), its successors and assigns, Assignor's entire right, title and interest in and to the following rights, interest, and property (hereinafter collectively called the "Rights"):

1. Assignor's invention of uses, methods and therapies of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, including without limitation Assignor's rights, powers, interests and title in and to the methods, uses and processes described in Schedule 1 attached to this Assignment, (collectively, herein called the "Invention").

2. All applications for patent or like protection on said Invention that have been or may in the future be made by Assignor or Assignor's legal representatives, in any and all countries.
3. All patents and like protection that have been or may in the future be granted on said Invention to Assignor or Assignor's legal representatives, in any and all countries of the world.
4. All substitutions for and divisions, continuations, continuations-in-part, renewals, reissues, extensions and the like of said applications and patents and similar rights or grants, including, without limitation, those obtained or permissible under past, present and future law and statutes.
5. All rights of action on account of past, present and future authorized or unauthorized use of said Invention and for infringement of said patents and like protection.
6. The right of Assignee to file in his name disclosure documents, applications for patents and like protection for said Invention in any country and countries in the world.
7. All international rights of priority associated with said Invention, disclosure filings, applications, patents and like protection.

TO HAVE AND TO HOLD the Rights unto the Assignee, its successors and assigns forever, and Assignor does hereby bind himself, his heirs, legal representatives and assigns, to forever WARRANT and DEFEND the title to the Rights unto the said Assignee, its successors and assigns, against any person whomsoever lawfully claiming, or to claim the same, or any part thereof.

Assignor covenants and agrees that Assignor will cooperate with Assignee such that Assignee may enjoy to the fullest extent the benefit of this Assignment. Such cooperation shall include, but not limited to, all of the following:

1. Assignor's prompt execution of all papers that are deemed necessary or desirable by Assignee to perfect the right, title and

interest herein conveyed, and

2. Assignor's prompt execution of all petitions, oaths, specifications, declarations or other papers that are deemed necessary or desirable by Assignee for filing and prosecuting patent applications, for filing and prosecuting substitute, division, continuing, or additional applications in the United States and/or all foreign countries, for filing and prosecuting applications for reissuance or reexamination of letters patent, and for interference proceedings involving and covering any of the Rights, and

3. Assignor's prompt assistance and cooperation, including but not limited to execution of documents and testifying, in the prosecution of legal proceedings involving any of the Rights, including, but not limited to, patent prosecution, interference proceedings, infringement court actions, opposition proceedings, cancellation proceedings, priority contests, unfair competition court actions, trade secret court actions, public use proceedings, slander, license breach and royalty collection proceedings and other legal proceedings.

Assignor warrants that Assignor has the right to make the assignment set forth herein and that no other person or entity has any rights of ownership or claim to the subject matter of this Assignment as of the date of this Assignment. This Assignment is binding upon Assignor, Assignor's heirs, administrators, executors, successors, trustees, devisees and assigns and inures to and for the benefit of Assignee, its successors and assigns.

EXECUTED effective as of the date first above written and at
the time and place indicated below opposite the signature:

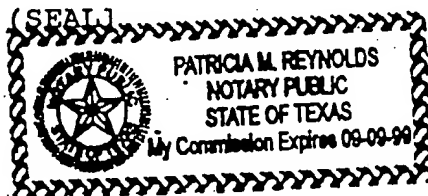
Woodie Roy
WOODIE ROY

Date: 7-24-98

STATE OF TEXAS §
 §
COUNTY OF BOWIE §

BEFORE ME, the undersigned authority, on this day personally
appeared WOODIE ROY known to me to be the person whose name is
subscribed to the foregoing instrument, and acknowledged to me that
she executed the same for the purposes and consideration therein
expressed.

GIVEN UNDER MY HAND AND SEAL OF OFFICE, this the 24th day
of July, 1998.



Patricia M. Reynolds
Notary Public Signature

PATRICIA M. REYNOLDS
Notary Printed Name

Commission Expires: 9/9/99

SCHEDULE 1 TO ASSIGNMENT

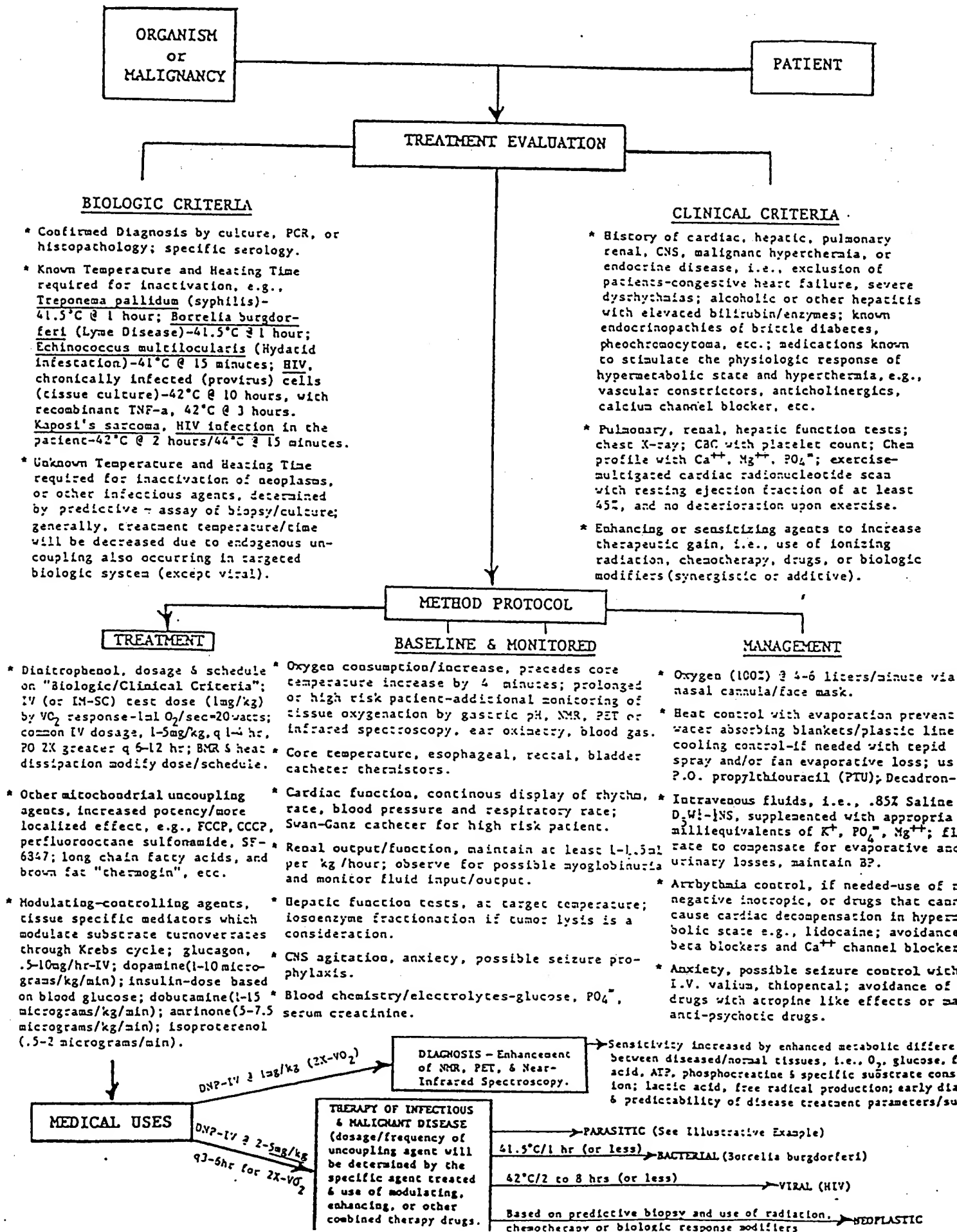
INVENTION

This invention provides a medical method for: (1) prevention of life threatening hypothermia; (2) enhancing magnetic resonance spectroscopy and positron emission tomographic metabolic imaging; and (3) treatment of resistant neoplastic and infectious disease by concurrent administration of dinitrophenol [or other mitochondrial thermoregulatory uncoupling agents, e.g., carbonylcyanide m-chlorophenylhydrazine (CCCP), carbonylcyanide-p-trifluoromethoxy-phenylhydrazine (FCCP), recombinant brown fat type protein, or lipid proton ionophores] and respiratory oxygen, intravenous fluids, anti-platelet drugs, as needed cooling, and specific metabolic, activating cytokines [e.g., recombinant tumor necrosis factor (TNF), interferons, etc.], hormones (e.g., glucagon), and other medications to control and focally enhance the mitochondrial uncoupling effects.

The present invention avoids the use of labor intensive, complex hyperthermia equipment, including invasive extracorporeal perfusion, with its associated thermal gradient toxicity problems to interposed normal tissues, inherent to all therapeutic methods of delivering heat from the outside-in. A new use(s)/method of generating intracellular oxygen derived free radicals, and heating from within the cell has been discovered for dinitrophenol (or other oxidative phosphorylation uncouplers) in prevention of cold injury, and treatment of free radical-thermosensitive parasites (e.g., Echinococcus), bacteria (e.g., Borrelia burgdorferi), lipid enveloped viruses (e.g., HIV), and neoplasia (e.g., gastric adenocarcinoma). It has further been discovered that cataracts, induced by dinitrophenol in the treatment of chronic obesity, can be prevented by concomitant administration of a variety of free radical scavenging agents, including tocopherol, ascorbic acid, and beta-carotene.

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A 52 year old white Swiss male, hunting dog trainer, presented with right upper quadrant abdominal pain. History revealed past (24 month old) hepatic "cyst" surgery and treatment with albendazole (only 1 dose was given because of anaphylactic reaction). He denied history of weight loss, pulmonary, cardiac or neurologic disease. Upon physical examination, he had a weight of 198 pounds (90 Kg), height of 5'11", blood pressure 140/80, pulse-76 and regular, respirations 18/minute, and oral temperature of 37.3°C. Laboratory studies, including hepatic, renal, pulmonary and cardiac function tests were normal; complete blood count was unremarkable except for 20% eosinophilia. Ultrasound and nuclear magnetic resonance of the liver revealed 4 (2-3 cm. in diameter) cysts in the mid-right lobe; ELISA serology showed a diagnostic titer specific for Hydatid disease with *Echinococcus multilocularis*. The patient refused to entertain any additional surgery or albendazole therapy.

After clinical assessment and treatment evaluation, i.e., *Echinococcus multilocularis* protoscoleces and germinal layers are destroyed at 41°C/15 minutes, whereas liver-hepatocytes withstand temperatures of 42°C to 44°C for known periods of 20 hours and 15 minutes respectively, the patient was given 1 aspirin; 10 mg. diazepam by mouth; and, intravenous fluids of 0.85 normal saline containing 9 millimolar K_2PO_4 , 7 milliequivalents of K^+ , and 2cc of 50% saturated solution of Mg_2SO_4 /liter, were infused at a rate of 12cc/kg/hr. Urine output was maintained at 1cc/kg/hour or greater. Esophageal (optional), rectal and foley (16 gauge) tipped bladder catheter thermistors gave temperature readings every two minutes within 0.1°C. Cardiac rate, rhythm, blood pressure, and respiratory rate sensors were placed and continuously displayed on a multi-channel monitor. Intravenous glucagon-2mg/hr was infused, with 1 mg given prior to DNP.

The patient was covered with a water absorbing polyethylene lined blanket, and baseline respiratory gas flow/oxygen consumption (VO_2) was determined using a 3 minute bag collection. Five minutes after intravenous administration of 90 mg of dinitrophenol (2% DNP/5% $NaHCO_3$ at 1 mg/kg), and determination that there was no untoward or idiosyncratic reaction, an additional 90 mg of 2,4 dinitrophenol (total of 180mg, 2mg/kg body weight) was infused. Monitored physiologic parameters are shown in the Table below. An additional VO_2 rate was obtained five minutes after the second dose of DNP and the patient was thereafter placed on 100% O_2 via nasal cannula. Target core temperature was maintained by occasional exposure of a limb and/or decreasing the glucagon infusion rate to 0.25 mg/hour. After the patient was maintained at a core temperature of 41.3°C for 20 minutes, the treatment was terminated by removing the blanket and permitting evaporative and radiant heat loss to return the body temperature to a normothermic level.

TABLE

Monitored Clinical Data On Mitochondrial Uncoupling Use/Method In Illustrative Example
(Treatment of Hydatid disease-*Echinococcus multilocularis*)

Time (minutes)	Medication (type & dose)	Resp. Rate- O_2 Consumption (breaths/min) ¹	Consumption (ml/min)	Cardiac Rate (beats/min)	Urine Output (total ml)	Core Temp. (°C)	Other (remarks)
-60	I.V. Fluids - 0.85 NS @ 0.8 L/hour	18	290	78	-	37.1	Fluids @ 10-12cc per kg/hour.
-30	Glucagon-IV drip @ 2mg/hour	20	-	79	27	37.1	Hepatic Krebs Cycle stimulation.
0	2,4-dinitrophenol-90mg IV in 4.5ml of 5% $NaHCO_3$ (prepared by dissolving 2.3gm DNP (13% H_2O) in 5% $NaHCO_3$ -giving 2% solution)	20	-	88	33	37.4	Covered with polyethylene blanket.
2		24	350	92	-	37.8	Increased O_2 consumption precedes temp. elevation.
5	2,4-dinitrophenol-90mg IV in 4.5ml of 5% $NaHCO_3$	26	-	98	-	37.8	
10	Fluids increased to 1.2 L/hour; start O_2	30	630	110	15	39.4	After VO_2 determined 100% O_2 @ 4 L/min via nasal cannula.
20	-	30	-	120	18	40.3	
40	Glucagon-IV drip decreased to 0.5mg/hr	30	-	134	25	41.4	Lower extremity is partially exposed.
60	Glucagon discontinued	30	-	140	30	41.2	Blanket removed
120	IV fluid discontinued	24	-	100	93	38.4	All thermistors removed

¹ Variations of the above use/method, i.e., protocol evaluation, monitoring, medications/dosages, time & temperature of mitochondrial uncoupling, will be necessitated by clinical and targeted biologic system treatment factors. Such variations for treatment of other parasitic (e.g., Malaria), bacterial (e.g., Lyme, Mansas disease), viral (e.g., HIV) and neoplastic disease will occur to those skilled in the art of medicine, and will be more fully described in the patent application.

The stamp of the PATENT OFFICE, placed hereon, acknowledges receipt of:

Applicant Bachynsky et al. By Fox/Delgado
Serial No. PCT/US99/16940 Atty Docket # P01615W00
Deposit/Mail Date 07/17/2000 Client # 09805783 CtxPharmaceutical

- | | |
|--|--|
| <input type="checkbox"/> Amendment | <input type="checkbox"/> Information Disclosure Statement |
| <input type="checkbox"/> Amendment after Final | <input type="checkbox"/> Form PTO-1449, References |
| <input type="checkbox"/> Appeal Brief, <u>0</u> Copies | <input type="checkbox"/> Issue Fee Transmittal |
| <input type="checkbox"/> Application for Patent including
<u>0</u> Pgs Spec., <u>0</u> Claims | <input type="checkbox"/> Notice of Appeal |
| <input checked="" type="checkbox"/> Assignments (1 for Bachynsky; 1 for Roy) | <input checked="" type="checkbox"/> Postcard |
| <input checked="" type="checkbox"/> Assignment Cvr Page (Form PTO-1595) 1 ea. | <input type="checkbox"/> Power of Attorney by Assignee(s) |
| <input type="checkbox"/> Cert. Of Exp. Mail under 37 CFR § 1.10 | <input type="checkbox"/> Power of Attorney by Inventor(s) |
| Express Mail No. _____ | <input type="checkbox"/> Preliminary Amendment |
| <input checked="" type="checkbox"/> Cert. Of Mailing under 37 CFR § 1.8(a) | <input type="checkbox"/> Priority Document |
| <input checked="" type="checkbox"/> Check for \$ 80.00 | <input type="checkbox"/> Req. for Filing [Cont.] [CIP] [Div. App.]
p.] under 37 CFR § 1.53(b) |
| | Filing CPA under CFR § 1.53(d) |
| | ion of Missing Parts |
| | ttal Letter (In duplicate) |
| | Statement to Establish Small Entity |

The stamp of the PATENT OFFICE, placed hereon, acknowledges receipt of:

Applicant Bachynsky et al. By Fox/Delgado
Serial No. PCT/US99/16940 Atty Docket # P01615W00
Deposit/Mail Date 07/17/2000 Client # 09805783 CtxPharmaceutical

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|--|---|
| <input type="checkbox"/> Amendment | <input type="checkbox"/> Information Disclosure Statement |
| <input type="checkbox"/> Amendment after Final | <input type="checkbox"/> Form PTO-1449, References |
| <input type="checkbox"/> Appeal Brief, <u>0</u> Copies | <input type="checkbox"/> Issue Fee Transmittal |
| <input type="checkbox"/> Application for Patent including
<u>0</u> Pgs Spec., <u>0</u> Claims | <input type="checkbox"/> Notice of Appeal |
| <input checked="" type="checkbox"/> Assignments (1 for Bachynsky; 1 for Roy) | <input checked="" type="checkbox"/> Postcard |
| <input checked="" type="checkbox"/> Assignment Cvr Page (Form PTO-1595) 1 ea. | <input type="checkbox"/> Power of Attorney by Assignee(s) |
| <input type="checkbox"/> Cert. Of Exp. Mail under 37 CFR § 1.10 | <input type="checkbox"/> Power of Attorney by Inventor(s) |
| Express Mail No. _____ | <input type="checkbox"/> Preliminary Amendment |
| <input checked="" type="checkbox"/> Cert. Of Mailing under 37 CFR § 1.8(a) | <input type="checkbox"/> Priority Document |
| <input checked="" type="checkbox"/> Check for \$ 80.00 | <input type="checkbox"/> Req. for Filing [Cont.] [CIP] [Div. App.]
[New App.] under 37 CFR § 1.53(b) |
| <input type="checkbox"/> Deposit Account No. 06-02375 for \$ _____ | <input type="checkbox"/> Req. for Filing CPA under CFR § 1.53(d) |
| <input type="checkbox"/> Declaration | <input type="checkbox"/> Submission of Missing Parts |
| <input type="checkbox"/> Drawings <u>0</u> Sheets,
<u>0</u> formal; <u>0</u> Informal | <input checked="" type="checkbox"/> Transmittal Letter (In duplicate) |
| <input type="checkbox"/> Extension of Time | <input type="checkbox"/> Verified Statement to Establish Small Entity |
| <input type="checkbox"/> Other _____ | |

424 Rec'd PCT/PTO 21 JUL 2000

Rec'd T/PTO 05 SEP 2001



Exhibit 2

INVENTOR DECLARATION

SEP 05 2001

Attorney Docket No.

985783 (P016115 US 0)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "Chemically Induced Intracellular Hyperthermia", the specification of which

(check one) ☒ is attached hereto.
☐ was filed on _____ as Application Serial No. or PCT international application No. [_____] and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
_____	_____
_____	_____

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s), or § 365(b) of any PCT international application designating the United States of America, listed below and insofar as the subject matter of each of the claims of this application is not disclosed in the prior U.S. or PCT international application in the manner provided by the first paragraph of Title 35, U.S.C. § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
_____	_____	_____
_____	_____	_____

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NE

Full Name of Sole or First Inventor Nicholas Bachynsky	Inventor's Signature <i>Nicholas Bachynsky</i>	Date 7-24-98
Residence Texarkana, Texas	Citizenship U.S.	
Post Office Address Same as above		

Full Name of Second Inventor Woodie Roy	Inventor's Signature <i>Woodie Roy</i>	Date 7-24-98
Residence	Citizenship U.S.	
Post Office Address Same as above		

Full Name of Third Inventor	Inventor's Signature	Date
Residence	Citizenship	
Post Office Address		

Full Name of Fourth Inventor	Inventor's Signature	Date
Residence	Citizenship	
Post Office Address		

Full Name of Fifth Inventor	Inventor's Signature	Date
Residence	Citizenship	
Post Office Address		

Full Name of Sixth Inventor	Inventor's Signature	Date
Residence	Citizenship	
Post Office Address		

Full Name of Seventh Inventor	Inventor's Signature	Date
Residence	Citizenship	
Post Office Address		

Full Name of Eighth Inventor	Inventor's Signature	Date
Residence	Citizenship	
Post Office Address		

#4



Please type a plus sign (+) inside this box



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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION FOR PATENT APPLICATION English Language Declaration (37 CFR 1.16(e))

☐ Declaration
Submitted
with Initial
Filing

☒ Declaration
Submitted after Initial
Filing (surcharge
(37 CFR 1.16 (e))
required)

Attorney Docket Number HO-P01615US1

First Named Inventor Nicholas Bachynsky

COMPLETE IF KNOWN

Application Number 09/744,622

Filing Date January 26, 2001

Group Art Unit N/A

Examiner Name Not Yet Assigned

As a below named assignee, I hereby declare that:

My mailing address is stated below.

As assignee, it is believed that the inventors, Nicholas Bachynsky and Woodie Roy, are the original and first inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

CHEMICALLY INDUCED INTRACELLULAR HYPERTHERMIA

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 01/26/2001 as United States Application Number or PCT International

Application No. 09/744,622 and was amended on (MM/DD/YYYY) (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached?	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority data sheet PTO/SB/026 attached hereto.

Declaration for Utility or Design Patent Application

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airmail No. _____, in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date shown below.

Dated: September 5, 2001

Signature: _____

(Paul E. Krieger)

By 1625, 586



I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/094,286</u> (Application No.)	<u>07/27/98</u> (Filing Date)
<u> </u> (Application No.)	<u> </u> (Filing Date)
<u> </u> (Application No.)	<u> </u> (Filing Date)

☐ Additional U.S. provisional applications are listed on a supplemental data sheet attached hereto.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

TEXAS PHARMACEUTICALS, INC. (Assignee)

BY: 

Name:

Title:

James J. Naples
President

Address: 701 W. 14th Street
Texarkana, Texas 75501

Date:

9-4-01